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What causes schizophrenia?

Schizophrenia remains unexplained. None of the abnormalities reported in the brains of schizophrenics is clearly diagnostic for the disease in the way that (say) plaques and tangles are for Alzheimer's disease. In the absence of a clear cellular pathology, the main clues as to the cause are epidemiological. There is general agreement that genes and environment are both involved; however, no genes have yet been identified, while most of the reported environmental influences are tentative hypotheses at best.

A recent paper[1], based on a very large cohort from Denmark, provides what may be the most comprehensive picture to date of the epidemiology of schizophrenia. The authors took advantage of the excellent civil registry and health care records in that country to analyze data from 1.75 million people, of whom 2669 developed schizophrenia; this sample included virtually every new case of schizophrenia between 1970 and 1993. The aim was to test the relative importance of some of the previously proposed risk factors in a large population.

The data confirm the well-known tendency for schizophrenia to run in families; individuals with a schizophrenic parent or sibling were almost ten times more likely to develop schizophrenia themselves, and for those with two affected parents the increase in risk was almost fifty-fold. The data also confirm a previously reported and puzzling season-of-birth effect; people born in March had a 10% elevated risk, whereas those born in September showed a correspondingly reduced risk. Perhaps most surprising is the effect of place of birth. Those born in the capital city, Copenhagen, had a 2.4-fold elevated risk compared to those born in rural areas, with intermediate risk factors for suburbs and provincial towns. (The risk was higher still for those born in Greenland—which belongs to Denmark—or in other countries, although sample sizes for those categories were relatively small.)

The implications become apparent when the numbers are translated into population attributable risk (PAR), which takes into account the number of people exposed to each risk factor. The factor with the greatest impact is place of birth, which the authors estimate accounts for 34.6% of the total PAR; the combined effect of place and season accounts for 41.4%. Taking these numbers at face value, if the environmental risk factor(s) could be identified and eliminated, 41.4% of cases of schizophrenia could be prevented. Given that schizophrenia is estimated to affect about 1% of the world's population, the potential implications are dramatic indeed.

Clearly these findings will require careful scrutiny. One concern with any registry-based study is the accuracy of the diagnosis, but Denmark has good psychiatric services, and most of the experts we consulted felt that diagnostic errors were unlikely to undermine the conclusions. A more serious concern arises from the distinction between risk attributable to family history and risk attributable to genotype as a whole. The authors conclude that family history accounts for only 5.5% of the total cases, far less than the 41% attributed to environmental factors. Yet the contribution of genotype as a whole may be much greater than the family history would suggest. Kenneth Kendler (Virginia Commonwealth University), who describes the data as "excellent", feels that the interpretation is flawed, because most people with a genetic vulnerability will not have an affected first-degree relative. Thus, although the authors may be technically correct in attributing only 5.5% of cases to the effect of parents and siblings, this is likely to substantially underestimate the importance of genetic effects. Bernard Devlin (University of Pittsburgh) agrees, and believes that the method used by the authors may also lead to an overestimate of the contribution of the environment. It is difficult to guess by how much, he says, but it would clearly be premature to conclude that any one environmental risk factor accounts for more cases than does genotype.

Nevertheless, the environmental effects are substantial and seem to demand explanation. One possibility is exposure to infection, either *in utero* or in early childhood; this would fit well with the effects of season and urbanization, and might also explain the effect of being born abroad, if for instance the mother is exposed to foreign pathogens to which she has less immunity. The evidence for the infection hypothesis, however, is still weak, according to Daniel Weinberger (National Institute of Mental Health), who believes that genetic explanations remain equally plausible; for instance, alleles that confer risk of schizophrenia on the offspring might also affect the behavior of their parents, making them more likely to migrate to cities, or more likely to mate in summer than in winter.

Further progress is likely to depend on the identification of susceptibility genes, which—given the promising signs from linkage studies—cannot be far away. It would be naive, however, to expect an early explanation of the disease, particularly given that even between monozygotic twins, concordance is only about 50%. Cloned genes might provide immediate insights (if, say, their expression is restricted to developing dopamine neurons), but this would be a stroke of luck indeed. Recall that the genes that cause familial Alzheimer's disease or Huntington's disease are ubiquitously expressed and have not yet led to a clear understanding of either disease process, despite a well-defined cellular pathology. The absence of such signs in schizophrenia may also be a problem in making animal models; how will we recognize a schizophrenic mouse?

The immediate impact of cloned genes will be on epidemiology, specifically on the ability to stratify the patient population by genotype to reveal environmental effects. Epidemiology in turn will provide important clues in the search for a cellular pathology; if, for instance, the effects of season and place of birth that are apparent in the Danish cohort really do signify a prenatal environmental influence, this should motivate an intensive study of brain development, and of the role of susceptibility genes, during the epidemiologically defined critical period.

1. Mortensen, P. B. *et al. N. Engl. J. Med.* **340**, 603–608 (1999).